REMARKS

Claims 1-18 and 20-68 are pending. The Examiner withdrew claims 51-67 from consideration. Claims 1-18, 20-50, and 68 are under consideration.

Applicants acknowledge the Examiner's statement of reasons for finding the subject matter of claims 26-50 allowable. *See* Office Action at page 6, item 7.

I. Rejection of Claims 1-18 and 20-68 Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-18 and 20-68 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Office Action at page 2, item 3. Applicants assume that the Examiner intended to reject claims 1-18, 20-50, and 68, in light of the fact that the Examiner withdrew claims 51-67 from consideration. Applicants will address the rejection based on that assumption.

The Examiner alleges the following grounds for rejection:

a) The Examiner contends that claims 1-18, 20-25, and 68 are allegedly vague and indefinite "because [of] the phrase 'directly sequencing.'" Office Action at page 2, item 3(a). Specifically, the Examiner stated that "[i]t is unclear what is the definition of the phrase." *Id.* Applicants amended claims 1 and 68 to recite "directly sequencing" in the Amendment and Response filed September 15, 2004. Applicants note that the Examiner did not reject the claims under 35 U.S.C. § 112, second paragraph, for reciting "directly sequencing" in the Office Action mailed thereafter on December 3, 2004.

"The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed." MPEP § 2173.05(a) (8th ed. rev. 2 May 2004). Applicants assert that the meaning of the term "directly sequencing" is apparent from the specification. For example, the specification states that "[a]mplified product...could directly be used in sequencing reactions, while the amplified product subjected to electrophoresis could not be further analyzed without an additional purification step." Specification at page 18, para. 53. The specification then provides an example in which an amplification product is directly sequenced. Specification at page 18, para. 54. In that example, the amplification product is not subject to purification prior to sequencing. *Id.* Thus, it is apparent that "directly sequencing" means that an amplification product is not subject to purification prior to sequencing.

Claims 1 and 68, which recite the term "directly sequencing," are therefore clear and definite. Claims 2-18 and 20-25 ultimately depend from claim 1. Thus, those claims are also clear and definite.

b) The Examiner contends that claims 26-50 are allegedly vague and indefinite "because it is unclear whether or not the target polynucleotide are the same in the first reaction composition and the second reaction composition." Office Action at page 3, item 3(b). Claim 26 recites "a first reaction composition and second reaction composition, both specific for the at least one target polynucleotide...." *See* Amendment and Response to Final Office Action filed March 2, 2005, at page 6, lines 4-5 of claim 26. Claim 26 further recites "amplifying the at least one target polynucleotide present in the reaction compositions...." *Id.*, lines 11-12 of claim 26. The term "the at

least one target polynucleotide" has antecedent basis in the preamble of claim 26, which recites "[a] method of determining the presence and sequence of at least one target polynucleotide in a sample...." *Id.*, lines 1-2 of claim 26.

Because "the at least one target polynucleotide" in the first reaction composition and "the at least one target polynucleotide" in the second reaction composition have the same antecedent basis, "the at least one target polynucleotide" is the same in the first and second reaction compositions. More specifically, because the first reaction composition and the second reaction composition are "separate reaction compositions" (see *id.*, lines 9-10 of claim 26), one skilled in the art would understand that "the at least one target polynucleotide" in the first reaction composition comprises the same nucleic acid sequence, but is a separate nucleic acid molecule, relative to "the at least one target polynucleotide" in the second reaction composition.

Claim 26 is therefore clear and definite. Claims 27-50 ultimately depend from claim 26. Thus, those claims are also clear and definite.

c) The Examiner contends that claims 26-50 are allegedly vague and indefinite "because it is unclear how the target polynucleotide in the first reaction composition is detected since there is no detectable indicator in the first reaction composition." Office Action at page 3, item 3(c).

The Examiner imposed this same rejection in the Office Action mailed February 11, 2003, at page 2, item 2(b). The Examiner reiterated and further explained that rejection in the Advisory Action mailed September 24, 2003, as follows:

> ...[i]t is still unclear how the sequence of the at least one amplification product of the first reaction composition is determined since the first reaction composition does not [have] a fluorescence indicator.
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> *****

> ...[i]t is unclear how to determine whether the at least one amplification product is present in both the first reaction composition and the second reaction composition from the intensity of signal from the fluorescent indicator in the second reaction composition. [In other] words, there is no a [sic] relation between the first composition and second composition.

Advisory Action mailed September 24, 2003, at pages 2-3.

Applicants argued against this rejection in the Amendment and Response filed February 11, 2004. Specifically, Applicants explained how the relationship between the first and second reaction compositions allows one to determine whether the at least one amplification product is present in the first reaction composition based on the intensity of signal from the fluorescent indicator in the second reaction composition. *See* Amendment and Response filed February 11, 2004, Section II, pages 15-16. That argument is reproduced below:

> The relationship between the first and second reaction compositions is clearly set forth in the claims. Nucleic acid from the same sample is combined with the first and second reaction compositions. Both reaction compositions are "specific for the at least one target polynucleotide," and both comprise "amplification primers specific to the at least one target polynucleotide." Thus, one can determine whether the at least one amplification product is present in the first reaction composition based on the intensity of signal from the fluorescent indicator in the second reaction composition, because of the above relationship between the first and second reaction compositions.

Id. at page 16. The Examiner expressly withdrew the rejection in the Office Action mailed June 15, 2004, at page 2, item 2.

For at least the reasons which are already of record in the Amendment and Response filed February 11, 2004, and which are reiterated above, Applicants assert that claims 26-50 are clear and definite.

In summary, claims 1-18, 20-50, and 68 are clear and definite for at least the reasons discussed above in items (a), (b), and (c). Withdrawal of the rejection of those claims under 35 U.S.C. § 112, second paragraph, is respectfully requested.

II. Rejection of Claims 1-18, 20-25, and 68 Under 35 U.S.C. § 103(a)

The Examiner maintained the rejection of claims 1-18, 20-25, and 68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pritham et al. (J. Clinical Ligand Assay (1998) 4:404-412), in view of Johnston-Dow et al. (U.S. Patent No. 6,103,465). Office Action at page 3, item 5. Applicants respectfully traverse this rejection.

Applicants responded to this rejection in the Amendment and Response to Final Office Action filed March 2, 2005. *See* Amendment and Response to Final Office Action filed March 2, 2005, at pages 14-18, incorporated herein by reference. In considering Applicants' response, the Examiner states that the Applicants' arguments are allegedly based on limitations not recited in the claims. *See* Office Action at page 5. Specifically, the Examiner characterizes the Applicants' arguments as follows:

> The response argues that it would have been unpredictable at the time the invention was made whether an amplified product could be directly sequenced in the presence of a [fluorescent] indicator that is "a nucleic acid binding molecule" or in the presence of "an intercalating fluorescent indicator." *However, the limitations discussed herein are not in the claims.*
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> *****
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> The response also argues that directly sequencing the amplification product in the presence of a fluorescent indicator that binds nucleic acid might have been "obvious to try." *However, the limitation discussed herein is not in the claims.*
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> *****

> The response further argues that the Applicant's own work "direct sequencing of an amplification product in the presence of a fluorescent nucleic acid binding molecule" is not a reasonable expectation of success. *However, the limitation discussed herein is not in the claims.*

Office Action at page 5 (emphasis added).

Applicants respectfully point out that the Examiner is incorrect. Claim 1 recites the element "wherein the fluorescent indicator is a nucleic acid binding molecule." *See* Amendment and Response to Final Office Action filed March 2, 2005, at page 2, lines 4-5 of claim 1. Accordingly, claims 2-18 and 20-25, which ultimately depend from claim 1, also include that element. Furthermore, claim 68 recites "an intercalating fluorescent indicator." *Id.* at page 13, line 4 of claim 68. Thus, the Examiner is incorrect in stating that those elements are "not in the claims."

Thus, Applicants respectfully request that the Examiner reconsider the arguments made in the Amendment and Response to Final Office Action filed March 2, 2005, in light of the fact that the elements discussed in those arguments are indeed recited in the claims.

The Examiner further alleges that "the limitation 'directly sequenced' is unclear...." Office Action at pages 5-6. For at least the reasons set forth above in Section I, Applicants assert that the term "directly sequencing," which is recited in claims 1 and 68, is clear and definite.

Finally, the Examiner contends that "the specification discloses that in certain embodiments, one does not actually sequence the amplification product from the reaction composition that includes the fluorescent indicator (See pg.14, paragraph 042)." Office Action at page 5. Although the specification discloses that embodiment, neither claim 1 nor claim 68 encompasses that embodiment. Claim 1 recites that the "at

least one reaction composition compris[es] a fluorescent indicator...and amplification primers...." Claim 1 further recites "amplifying the at least one target polynucleotide present in the reaction composition using the amplification primers to obtain at least one amplification product...; and directly sequencing the at least one amplification product...." Thus, it is clear from the express language of claim 1 that "the at least one amplification product" that is directly sequenced is from the reaction composition comprising the fluorescent indicator.

Similarly, claim 68 recites that the "at least one reaction composition compris[es] an intercalating fluorescent indicator...and amplification primers...." Claim 68 further recites "amplifying by polymerase chain reaction the at least one target polynucleotide present in the reaction composition using the amplification primers to obtain at least one amplification product...; [and] directly sequencing the at least one amplification product...." Thus, it is clear from the express language of claim 68 that "the at least one amplification product" that is directly sequenced is from the reaction composition comprising the intercalating fluorescent indicator.

For at least the foregoing reasons, the Examiner has failed to establish that claims 1 and 68 would have been obvious over Pritham in view of Johnston-Dow. Claims 2-18 and 20-25 ultimately depend from claim 1. Thus, those claims would not have been obvious over Pritham in view of Johnston-Dow. Applicants respectfully request withdrawal of the rejection of claims 1-18, 20-25 and 68 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the application. In the event that the Examiner does not find the claims allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6778 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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